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THE MANUFACTURE AND STUDY OF STROMA FREE HEMOGLOBIN SOLUTION.(U)
SEP 76 G S MOSS DADA17-71-C-1106
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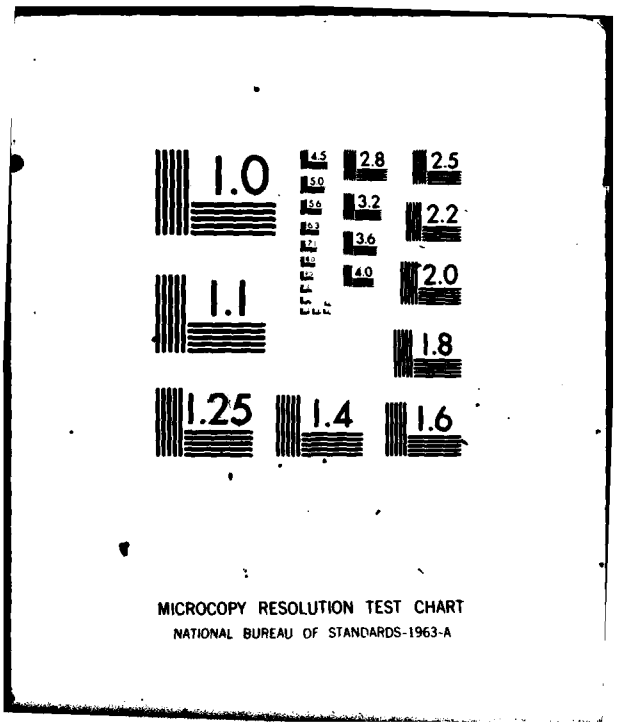
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THE MANUFACTURE AND STUDY OF HEMOGLOBIN - SALINE SOLUTION

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BEFORE COMPLETING FORM

1. REPORT NUMBER	2. GOVT ACCESSION NO.	3. RECIPIENT'S CATALOG NUMBER
24	AD-A096 189	

4. TITLE (and Subtitle)

(6) The Manufacture and Study of Stroma Free Hemoglobin Solution.

5. TYPE OF REPORT & PERIOD COVERED
Renewal Request
1/1/77 - 12/31/77

6. PERFORMING ORG. REPORT NUMBER

7. AUTHOR(s)

(19) Gerald S. Moss M.D.

8. CONTRACT OR GRANT NUMBER(s)

(15) DADA-17-71-C-1106

9. PERFORMING ORGANIZATION NAME AND ADDRESS
Hektoen Institute for Medical Research
627 South Wood Street
Chicago, Illinois 60612

10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS
DD Form 1498
Res. and Tech. Work Unit Summary

11. CONTROLLING OFFICE NAME AND ADDRESS
Headquarters, Dept. of the Army, U.S. Army Med Res. and Dev. Command, Washington, D.C.
HQDA (SGRD-RP) Washington, D.C. 20314

(11)

12. REPORT DATE
(10) Sep[redacted]76

13. NUMBER OF PAGES

14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office)

15. SECURITY CLASS. (of this report)
(12) 12

15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release, distribution limited.

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

(9) Rept. no. 24, 1 Jan - 31 Dec 77,

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

Hemoglobin-Saline Solution, Cardiac Output, Isoproterenol, Primate

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Primates exchange transfused to 6 gms % native hemoglobin can be stimulated to increase their cardiac output by 60%. Primates exchange transfused to 6 gms % foreign hemoglobin can be stimulated to raise their cardiac output by 40%.

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SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

A. STUDIES COMPLETED THIS YEAR

1. The Effect of Stroma Free Hemoglobin on the Heart

INTRODUCTION

Primates exchange transfused to zero hematocrit with a modified red cell hemolysate maintain normal oxygen consumption. Their hemoglobin mass was reduced to 6 grams %, and the P_{50} was decreased to 14 mm Hg. Oxygen consumption was maintained by increasing the extraction ratio, with no change in cardiac output. This was surprising to us since the typical response to hemodilution is an increase in cardiac output. Some form of hypoxic heart failure could have been responsible or these animals might not have had sufficient stimulus to increase their cardiac output.

The purpose of the current study was to evaluate the ability of such animals to increase their cardiac output in response to β-adrenergic stimulation. This was accomplished by using a standardized bolus infusion of isoproterenol. It has been shown that the hypoxic and ischemic myocardium has an altered response to this drug.

METHODS AND MATERIALS

Eight adult baboons weighing from 13.5 to 21.8 kg were the test animals. Approximately ten days before the study an electromagnetic flow probe was placed around the ascending aorta, and the leads were buried subcutaneously. On the morning of each study, the baboon was tranquilized within its cage with an intramuscular injection of 0.8 mg/kg of phencyclidine hydrochloride piperazine. Under local anesthesia, four plastic catheters were inserted in bilateral femoral arteries and veins and positioned in the inferior vena cava and the abdominal aorta. One pair was connected to Statham pressure transducers and monitored aortic and central venous blood pressures. The other pair was used for the exchange transfusion and for venous infusion of isoproterenol. The leads from the flow probe were exposed and connected to a Micron RC-1000 electromagnetic flowmeter. A lead II EKG was obtained with needle electrodes. The flow signal was integrated by an analog integrator and the output analyzed by a minicomputer to yield stroke volume. The signals from all transducers were recorded on a Brush multichannel oscillograph. A temperature probe was positioned in the abdominal cavity through a small incision in the abdominal wall. The trachea was intubated and the baboon was paralyzed by frequent intravenous injections of d-tubocurarine. The baboon was mechanically ventilated with room air in the prone position. In the base line period the tidal volume and respiratory rate were adjusted to produce an arterial pCO_2 between 33 and 47 mm Hg. These ventilator settings were held constant through each study.

The body temperature was kept constant by raising the ambient temperature.

A continuous monitor of CVP, arterial pressure, stroke volume, heart rate, and cardiac output was started. After several minutes of control data the animal was given an I.V. bolus infusion of 2 mcg/kg of isoproterenol.

The monitoring was continued until the variables returned to baseline values. A minimum of 45 minutes was provided for recovery from the injection. The animals received two subsequent infusions of isoproterenol. The protocol required about three hours to complete.

The eight baboons were randomly assigned to two groups of four each. Those in one group were exchange transfused with the modified hemolysate solution and those in the other group were exchange transfused with Dextran-75. In each baboon, blood was withdrawn in 50 milliliter aliquots from the arterial catheter and simultaneously replaced by a similar volume of test solution infused into the femoral vein. The exchange transfusion continued until the Dextran group reached a hematocrit of 20 (equivalent to a hemoglobin mass of 6 grams %) and hemolysate group reached a hematocrit below 2. At this point they had approximately equal hemoglobin masses. The animals were maintained at these hematocrits for three hours. After this period of time, they again were challenged with isoproterenol using an identical protocol. The total length of the procedure was approximately 12 hours.

At the conclusion of each experiment statistical analysis of the data was performed to determine whether or not additional animal experiments were necessary to reach a significant result. This was done to minimize the number of animals used.

RESULTS

Eleven primary and derived variables were analyzed. They are: peripheral resistance (PR), cardiac output (CO), stroke volume (SV), cardiac work (CW), peak aortic flow (PF), mean arterial pressure (MAP), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), heart rate (HR), central venous pressure (CVP), and stroke work (SW). All data was expressed as percentage change from the pre-isuprel state to the peak response immediately after isuprel. Table I contains the data for the Dextran group. Table II exhibits the results for the hemolysate group. In all cases a consistent qualitative pattern was exhibited. There were significant increases in cardiac output, heart rate, cardiac work and peak flow. There were significant decreases in peripheral resistance and diastolic arterial pressure. Stroke volume tended to increase slightly, as did CVP and stroke work. The mean arterial pressure exhibited a slight decrease and the systolic arterial pressure had a slight increase. All of these changes are consistent with the concept of isoproterenol as an almost pure β-agonist. In order to quantitatively compare the Dextran group with the hemolysate group, a sequence of analyses of variances was performed. Table III and IV contain the results of these analyses. Table IV shows that the Dextran exchange transfusion had no effect on the response to isoproterenol of SV, CO, DAP, MAP, SW, CW, PR, PF, and CVP. It had a small effect on SAP ($p = .04$) and a larger effect on HR ($p = .012$). If we used a $p<.01$ criterion, we could say that the Dextran exchange transfusion had no effect on any variable.

In the hemolysate group, the exchange transfusion had no effect on DAP, SAP, MAP, CW and CVP. It had a moderate effect on SV ($p = .013$), and PF ($P = .044$). It had a significant effect on HR ($p = .001$), CO ($p = .005$), SW ($p = .007$), and PR ($p = .003$). Table III indicates that during the control, or pre-exchange period, the two groups exhibited similar responses with report to CO, DAP, SAP, MAP, CW, PR and CVP. Slight differences were observed in the SW. Large differences were observed in the HR, SV and PF. Hence, the difference in pattern between the two groups is most consistent for the CO and PR, and less clear for the HR, SW, PF and SV.

Discussion

This study clearly indicates that there is a diminution of response in cardiac output and peripheral resistance after exchange transfusion with a modified hemolysate. However, it is by no means clear that this effect is large enough, or relevant to the constancy of cardiac output in our previous study. The increase in CO, after β-stimulation, went from 62% to 44% after transfusion. Hence, after 3 hours at 0 hematocrit these animals can increase their cardiac output by a factor of almost 1.5. We believe this demonstrates adequate reserve for adrenergic stimulation. The increase in cardiac output in the Dextran group was primarily a stroke volume, rather than a heart rate effect. Such increases in stroke volume are not associated with adrenergic stimulation; hence, it is possible that the animals receiving hemolysate failed to increase their cardiac output because of a depression of a non-adrenergic channel. A description of this possibility is not possible at this time.

Table I
Dextran Group
% Change Due to Isoproterenol

Variable	Before Dextran Exchange	After Dextran Exchange
Peripheral Resistance	-43%	-45%
Stroke Work	+13.5%	+15%
Central Venous Pressure	+14%	+8%
Heart Rate	+36%	+28%
Cardiac Output	65%	+61%
Stroke Volume	22%	27%
Cardiac Work	56%	42%
Peak Flow	61%	56%
Mean Arterial Pressure	-6.5%	-14.5%
Systolic Arterial Pressure	4.5%	-2%
Diastolic Arterial Pressure	-16%	-19.5%

Table II
Hemolysate Group
% Change Due to Isoprotesenol

Variable	Before Hemolysate Exchange	After Hemolysate Exchange
Peripheral Resistance	-43%	-30%
Stroke Work	-5%	+16%
Central Venous Pressure	+17.5%	-2%
Heart Rate	+58%	+23%
Cardiac Output	62.5%	44%
Stroke Volume	4.5%	18%
Cardiac Work	49.5%	42%
Peak Flow	46%	33%
Mean Arterial Pressure	-8%	-2%
Systolic Arterial Pressure	4%	11.5%
Diastolic Arterial Pressure	-18%	-15.5%

TABLE III

COMPARISON OF DEXTRAN VS. HEMOLYSATE GROUP

VARIABLE	BEFORE EXCHANGE TRANSFUSION		AFTER EXCHANGE TRANSFUSION	
	t	p	t	p
HR	- 7.00	<.001	1.92	.073
SV	6.60	<.001	2.46	.026
CO	0.38	.710	3.10	.007
DAP	0.36	.725	- .81	.431
SAP	.03	.979	- 4.58	<.001
MAP	0.26	.800	- 2.94	.010
SW	2.83	.012	- .65	.528
CW	0.36	.726	.02	.984
PR	- 0.05	.962	- 4.93	<.001
PF	5.84	<.001	4.51	<.001
CVP	N.S.	N.S.	N.S.	N.S.

TABLE IV

COMPARISON BEFORE VS. AFTER EXCHANGE

VARIABLE	DEXTRAN GROUP		HEMALYSATE GROUP	
	t	p	t	p
HR	- 2.77	.012	- 4.03	.001
SV	1.59	.129	2.72	.013
CO	- .61	.550	- 3.20	.005
DAP	.82	.420	.32	.753
SAP	- 2.18	.042	1.45	.164
MAP	- 1.60	0.129	1.09	.289
SW	- .27	.788	3.02	.007
CW	- 1.41	.176	- .62	.546
PR	- .77	.451	3.34	.003
PF	- 1.37	.187	- 3.16	.044
CVP	N.S.	N.S.	N.S.	N.S.